Petition for extension of time is due, this paper can be considered such Petition.

Claims 1-21 are presently pending in this application. Claim 1 is amended to more distinctly claim the subject matter by specifying that the second region contains a selectively chemically cleavable site. Claims 2 and 5-8 are amended to reflect the amendment of Claim 1. Basis for the amendment can be found, for example, in the specification at page 6, lines 8-9; page 28, lines 19-24; page 38, lines 12-16; page 39, lines 8-12; page 40, lines 27-28; page 41, lines 1-6; and page 43, lines 3-4 and 23-28, as well as in Examples 3-5.

A marked up copy per 37 C.F.R. §1.121 showing changes made to the claims is attached to this response.

THE REJECTION OF CLAIMS 1-9, 11-14, 20 and 21 UNDER 35 U.S.C. §102(e)

Claims 1-9, 11-14, 20 and 21 are rejected under 35 U.S.C. § 102(e) as anticipated by Köster *et al.* (U.S. Patent 5,622,824) because Köster *et al.* allegedly discloses a nucleic acid primer having a first region containing the 5' end of the primer and an immobilization attachment site, and a second region containing the 3' end of the primer and a chemically cleavable site, where the 3' end is capable of being extended by an enzyme. It is further alleged that the limitations of dependent claims 2-9, 11-14, 20 and 21 are inherent in the disclosure of Köster *et al.* and thus the disclosure of Köster *et al.* allegedly "anticipates the limitations" of claims 1-9, 11-14, 20 and 21." This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990); *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990); *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl. 1966). See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll

limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover, it is incumbent on the Examiner to identify where each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Independent claim 1 and its dependent claims (2-21) are directed to a nucleic acid primer having a 5' end and a 3' end, which includes a first region containing the 5' end of the primer and an immobilization attachment site; and a second region containing the 3' end of the primer and a *selectively chemically* cleavable site. The 3' end is capable of being extended by an enzyme to generate an extension segment. When the primer is immobilized via the immobilization attachment site, and the selectively chemically cleavable site is cleaved, the remainder of the primer remains immobilized.

DIFFERENCES BETWEEN THE CLAIMS AND THE TEACHINGS OF THE CITED REFERENCE

Köster *et al.* (5,622,824)

Köster *et al.* discloses a method of determining the sequence of a nucleic acid by *enzymatic sequential* directed digestion of the nucleic acid by exonucleases and identification of the sequentially released fragments using mass spectrometry (MS). The reference discloses the use of MALDI-TOF MS for analysis of biomolecules, using PCR methods to amplify test material, and use of exonucleases and mass-modified nucleoside triphosphates to modify the sample biomolecule prior to analysis. Köster discloses attaching a linear single-stranded DNA fragment to a solid support via its 5' end and attaching a target DNA to be

sequenced via a "splint oligonucleotide" containing sequences complementary to the bound DNA fragment and the DNA fragment to be sequenced. Köster discloses releasing nucleotides from the 3' end of the target DNA by contacting it with a 3'-exonuclease which digests the nucleotides. As demonstrated below, Köster does not disclose primers where the 3' end contains a selectively chemically cleavable site; the nucleic acid molecules are *enzymatically* and *sequentially* digested in the method of Köster.

ANALYSIS

Köster does not anticipate any of the instant claims, because Köster does not disclose primers with a 3' end that includes a *selectively chemically* cleavable site.

The Examiner appears to allege that degradation of the 3' end of the primer by a 3' exonuclease, as disclosed in Köster, is chemical cleavage of the primer "because the enzymatic cleavage involves a chemical reaction" (Advisory Action at page 2). Applicant maintains, however, that the term "chemically cleavable," as used in the specification and understood by those of ordinary skill in the art does ***not*** encompass enzymatic digestion (See, Amendment filed March 3, 2003, at pages 4-7; and U.S. Patent No. 5,547,835 to Köster *et al.*, at column 13, lines 15-36, and column 14, lines 18-23). Solely to advance prosecution of the present application, however, claim 1 has been amended to recite that the chemically cleavable site is *selectively chemically* cleavable. Basis for the amendment can be found throughout the specification. Specific support for the amendment can be found, for example, in the specification at page 6, lines 8-9; page 28, lines 19-24; page 38, lines 12-16; page 39, lines 8-12; page 40, lines 27-28; page 41, lines 1-6; and page 43, lines 3-4 and 23-28, as well as in Examples 3-5. In particular, for example, the specification states that "'[c]leavable site' as used herein is a reactive moiety typically...selectively cleavable by appropriate non-enzymatic or enzymatic means including chemical, thermal, or photolytic..." (Specification at page 28, lines 19-23).

Köster does ***not*** disclose a nucleic acid primer having a second region at the 3' portion that includes a *selectively chemically* cleavable site. Thus, the cited reference fails to disclose every element of the claimed subject matter. Accordingly, Köster does not anticipate any of claims 1-21.

THE REJECTION OF CLAIMS 15-19 UNDER 35 U.S.C. §103(a)

Claims 15-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Köster (U.S. Patent 5,622,824) in view of Köster (U.S. Patent 5,547,835) because Köster '824 allegedly teaches every element of the claimed subject matter except that the solid support includes a functionality selected from among avidin and streptavidin, and antibody and anti-antibody, but the Examiner alleges that Köster '835 cures this defect.

The rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. App. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" (*In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981)), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or

suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of prima facie obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963).

THE CLAIMS

Dependent claims 15-19 are directed to various embodiments of the primer of independent claim 1. For example, claim 15 is directed to a primer that includes a solid support, where the solid support includes a functionality selected from avidin and streptavidin. Claim 16 is directed to a primer that includes a solid support, where the solid support includes an antibody. Claim 17 depends from claim 16 and is directed to a primer where the antibody includes anti-digoxigenin. Claim 18 is directed to the primer of claim 1 where the immobilization attachment site is a substituent on one of the bases or sugars of the primer. Claim 19 is directed to the primer of claim 1 where the immobilization attachment site is biotin or digoxigenin.

Differences between the cit d references and the claimed subject matter

Köster (U.S. Patent 5,622,824)

See related section above. As discussed above, Köster fails to disclose or teach a primer with a 3' end with a *selectively chemically* cleavable site.

Köster (U.S. Patent 5,547,835)

Köster '835 is directed to a mass spectrometric method for sequencing using a Sanger sequencing strategy, in which one embodiment includes immobilizing the sequencing primers to a support using various linkers. Köster '835 teaches that the primer has a linking functionality L at the 5'-end that interacts with a suitable functionality L' on the solid support to form a reversible linkage L-L' (col. 11, lines 52-56).

ANALYSIS

The claims are not *prima facie* obvious because the combination of teachings of Köster '824 with the teachings of Köster '835 does not result in the instantly claimed primers.

Claims 15-19 of the instant application are directed to various embodiments of the nucleic acid primer of claim 1. As discussed above, Köster '824 does not teach or suggest a nucleic acid primer that has a 5' portion, and a 3' portion that includes a *selectively chemically* cleavable site. Köster '835 does not cure these defects. Köster '835 teaches a nucleic acid primer that has a 5' end containing a linking functionality L, which can interact with a suitable functionality L' on a solid support to form a temporary reversible linkage, and a 3' end that is base-specifically terminated (col. 11, lines 52-56; Figure 1). This can be depicted as:

SS—L'-L—5'————————————————————3'—T.

Köster '835 does not teach or suggest a nucleic acid primer containing a second region containing the 3' end of the primer and a selectively chemically cleavable site, such that when the primer is immobilized, and the selectively chemically cleavable site is cleaved, the remainder of the primer remains immobilized.

Instead, Köster '835 teaches a cleavable L—L' linkage at the ***5' end*** of the nucleic acid primer, cleavage of which ***removes the entire primer from the solid support*** (column 11, line 52 - column 13, line 2). The only cleavable site taught or suggested by Köster '835 is the cleavable site at the 5' end of the primer. Hence, Köster '835 fails to teach a second region of a primer containing the 3' end and a selectively chemically cleavable site.

Since, Köster '835 fails to teach a second region of a primer containing the 3' end and a selectively chemically cleavable site, Köster '835 fails to cure the deficiencies in the teachings of Köster '824. The combination of teachings of Köster '824 and Köster '835 fails to result in the instantly claimed primers. The combination of the teachings of Köster '824 and Köster '835 does not teach or suggest a nucleic acid primer having a 5' end and a 3' end, which includes a first region containing the 5' end of the primer and an immobilization attachment site; and a second region containing the 3' end of the primer and a unique selectively chemically cleavable site and a 3' end that is capable of being extended by an enzyme to generate an extension segment. Therefore, the Office Action does not set forth a *prima facie* case of obviousness, and the rejection should be withdrawn.

THE REJECTION OF CLAIM 10 UNDER 35 U.S.C. §103(a)

Claim 10 is rejected under 35 U.S.C. §103(a) as being unpatentable over Köster (U.S. Patent 5,662,824) in view of Richards *et al.* (U.S. Patent 5,427,929) because Köster allegedly teaches every element of claims 1-9, 11-14, and 20-21, and although Köster does not teach the ligase enzyme of claim 10, the Examiner alleges that Richards *et al.* cures this defect.

The rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 10 depends from claim 1 and is directed to the primer of claim 1, wherein the 3' end is capable of being extended by a ligase.

Differences between the cited references and the claimed subject matter

Köster (U.S. Patent 5,622,824)

See related section above.

Richards *et al.* (U.S. Patent 5,427,929)

Richards *et al.* teaches a method for reducing carryover contamination in an amplification procedure by incorporating at least one modification into the amplification product to distinguish it from the target sequence and allow it to be identified as background contamination. The reference teaches including restriction endonuclease target sites as cleavable sites in the amplification products, and use of restriction endonucleases to cleave the resulting modified products (see, e.g., Figures 5-9, 12-15, and 19). Prior to further amplification, the sample is treated to cleave the contaminant amplification product so that it cannot be amplified in the new sample. The reference teaches a method of using ribonucleotide substitution at the 3'-end of an amplification product and then extending it using PCR or LCR so that the ribonucleotide substitution is internalized in the sequence (col. 17, lines 33-45 and line 65 through col. 18, line 13). Richards *et al.* teaches that it is preferred to locate the cleavable site modification near the middle of an amplification probe or primer so that disruption of hybridization will be minimized (col. 17, lines 19-22). Richards *et al.* teaches the introduction of a number of different types of modifications into the amplification product (col. 9, lines 24-27) and the number of modification sites incorporated into the amplification product may vary (col. 10, lines 7-10). Richards *et al.* teaches that the amplification product can be modified at or about any location other than the extending end of the primer that does not interfere with amplification, and in that case the modification should be modified at its 5' end (col. 11, lines 15-30).

Richards *et al.* does not teach or suggest a nucleic acid primer having a 5' end and a 3' end, including a first region containing the 5' end of the primer and an immobilization attachment site; and a second region containing the 3' end of the primer and a selectively chemically cleavable site.

ANALYSIS

The claims are not *prima facie* obvious because the combination of teachings of Köster '824 with the teachings of Richards does not result in the instantly claimed primers.

As discussed above, Köster '824 does not teach or suggest a nucleic acid primer that has a 5' portion, and 3' portion that includes a selectively chemically cleavable site. Richards, which does not teach or suggest a nucleic acid primer having a 5' end and a 3' end, including a first region containing the 5' end of the primer and an immobilization attachment site; and a second region containing the 3' end of the primer and a selectively chemically cleavable site, does not cure these defects.

Notwithstanding the above, there would have been no motivation to combine the teachings of Köster with those of Richards *et al.*

The Examiner contends that one of ordinary skill in the art at the time of the instant application would have been motivated to "use a ligase in a nucleic acid polymerization reaction as taught by Richards *et al.* because the method of Richards *et al.* is efficient and economy [*sic*] for reducing carryover contamination in an amplification procedure" (Official Action mailed April 10, 2002, citing the Abstract).

Richards *et al.* teaches that it is preferred to incorporate modification site(s) into the nucleic acid at locations "which, when cleaved, will result in the most complete destruction of the" nucleic acid (Column 12, line 66, through column 13, line 3). The purpose of the cleavable sites in Richards *et al.* is to assist in the degradation and elimination of the nucleic acids that contain the cleavable sites because these nucleic acids are seen as contaminants (Abstract).

Thus, the teachings of Richards *et al.* are directed toward eliminating as contaminants the nucleic acids containing cleavable sites.

In considering the prior art under 35 U.S.C. 103, the totality of the prior art must be considered. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). Köster is directed to nucleic acid sequencing methods using mass spectrometry. A method of sequencing a nucleic acid is not improved by eliminating that nucleic acid as a contaminant, regardless of whether or not the method of eliminating that contaminant is more economical or efficient. Thus, one skilled in the art seeking to sequence a nucleic acid would not be motivated to modify that nucleic acid according to the teachings of economically and efficiently eliminating nucleic acids as contaminants. Accordingly, one skilled in the art seeking to modify the teachings of Köster would not be motivated to modify the nucleotide sequenced according to the method of Köster with the economic and efficient contaminant elimination method of Richards *et al.* to form a primer.

"Under section 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so." *In re Fritch*, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (emphasis in original). "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, at 1783-84. Without the teachings of the prior art suggesting the combination, it is impermissible to pick and choose among isolated disclosures in the prior art to conclude that the claimed in subject matter is obvious. *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

Köster does not suggest that a nucleic acid to be sequenced should be modified in order for the nucleic acid to be more efficiently eliminated as a contaminant. Richards *et al.* does not suggest use of the method of eliminating contaminant nucleic acids in order to determine the sequence of the contaminant nucleic acid. Thus, neither of the cited references suggests

combining the teachings of Köster with the teachings of Richards *et al.* in forming the nucleic acid of claim 10. Without the teachings of the references suggesting the combination, it is impermissible to pick and choose from Köster and Richards *et al.* to conclude that the claimed primers are obvious. Accordingly, the Office Action has not set forth a *prima facie* case of obviousness of claim 10.

* * *

In view of the above remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Monforte *et al.*

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Michael Lough

MARKED UP CLAIMS IN ACCORDANCE WITH 37 C.F.R. § 1.121

Please amend Claims 1, 2, and 5-8 as follows:

1. (Amended) A nucleic acid primer having a 5′ end and a 3′ end, comprising:

(a) a first region containing the 5′ end of the primer and an immobilization attachment site; and

(b) a second region containing the 3′ end of the primer and a selectively chemically cleavable site, wherein the 3′ end is capable of being extended by an enzyme to generate an extension segment,

whereby, when the primer is immobilized via the immobilization attachment site, and the selectively chemically cleavable site is cleaved, the remainder of the primer remains immobilized.

2. (Amended) The primer of claim 1, wherein the selectively chemically cleavable site is located at or within about five nucleotides from the 3′ end of the primer.

5. (Amended) The primer of claim 1, wherein the selectively chemically cleavable site comprises a modified base, a modified sugar, or a chemically cleavable group incorporated into the phosphate backbone.

6. (Amended) The primer of claim 5, wherein the selectively chemically cleavable site comprises a modified sugar.

7. (Amended) The primer of claim 1, where the selectively chemically cleavable site is selected from the group consisting of dialkoxysilane, 3'-(S)-phosphorothioate, 5'-(S)-phosphorothioate, 3'-(N)-phosphoramidate, 5'-(N)-phosphoramidate, uracil, and ribose.

8. (Amended) The primer of claim 7, wherein the selectively chemically cleavable site is 3'-(S)-phosphorothioate or 5'-(S)-phosphorothioate.